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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JHK Law
P.O. Box 1078
La Canada, CA 91012-1078

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,408	PARK ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/5/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 9/7/05 is entered.

Claims 1-20 are presently pending.

Election/Restrictions

Applicant's election is noted, but it is noted that Examiner found no art on the claims, given the enablement rejection, below, and as such, the elections of species are withdrawn.

Information Disclosure Statement

Applicant's IDS of 8/5/03 has been considered and signed, however, Applicant has failed to provide the title in each citation, and thus, the references have been crossed-out as they are not in conformance with the requirements for listing on the front of any patent that may issue.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Breadth of the Claims

Applicant's claims 1-10 encompass reducing any inflammation of the kidney of any subject, comprising delivering to the kidney, by any method, a gene encoding an anti-inflammatory or immunosuppressant protein. Claims 2-3 and 9-10, limit the gene to encoding IL-1Ra, IL-4, IL-6, IL-10, IL16, or TGF-beta1. Claims 4-7 limit the gene to being within a vector, a viral vector, an adenovirus, an AAV, a retrovirus, or a plasmid. Claims 8-10 require the gene to be within any cell, which is transformed with the gene *in vitro*, then administered (a.k.a., *ex vivo* therapy).

Claims 11-13 encompass treating any nephritis in any subject with similar administrations as claim 1. Claims 12-13 limit the nephritis to any glomerulopathy or glomerulosclerosis.

Claims 14-17 encompass preventing nephritis in any patient predisposed to develop such a condition, comprising similar administrations as claim 1. Claim 15 limits the nephritis to glomerulsclerosis. Claims 16-17 parallel claims 2-3.

Claims 18-20 encompass a method of reducing excretion of polypeptides in the urine of any subject suffering from any renal disorder, comprising similar administrations as claim 1. Claims 19-20 parallel claims 2-3.

These methods are broad in scope, drawn to many species of animal, many forms of administration, many vector types, many transgenes, and many kidney disorders.

The Nature of the Invention

The nature of gene therapy is generally not enabling of new inventions in the field.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of

altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific GDNF proteins, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

Moreover, from Applicant's specification, it is clear that Applicant's claims wish to encompass any protein derived from the various immunosuppressant proteins, and the art with regard to making these proteins is similarly not reasonably predictable.

To wit, it has long been known how to mutate proteins, but it has been similarly long been known that such mutations are not reasonably predictive of activity for any particular protein. For example, Rudinger (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7 discusses the peptide hormones and the characteristics of amino acids as components of the peptide hormones (TITLE). (It is noted that Rudinger discusses peptide hormones, but the general areas of unpredictability are common to all proteins.) In doing so, Rudinger notes that many amino acids may be grouped according to general characteristic (pp. 1-3), and many of these are also classified in two or more classifications (p. 3). Hence, simple mutations of "type" are not reasonably predictable, because there are multiple types to any particular amino acid. Moreover, Rudinger finds that the context of any amino acid is important for structure (pp. 3-4), and that therefore, simple deletions, insertions, or substitutions are also not reasonably predictable, because not only is "type" important, but context is also important, having longer-range effects than that of simply type. Further, Rudinger discusses the mechanisms of information transfer (e.g, binding and effecting a receptor, which is analogous to any protein binding anything and causing any particular effect) (pp. 4-5). In doing so, Rudinger finds that there exist "patterns" on molecules for recognition, which may involve amino acids close by in the amino-acid polypeptide sequence, or far away (Id.). As such the conformation of the whole molecule is important, and any particular amino acid change, deletion, or addition,

may alter the conformation of the molecule enough to affect any particular binding and effect on another molecule.

> In analyzing the significance of such observations, Rudinger states that:
> In a given molecule, some amino acids or sequences obviously owe their 'significance' to their inclusion in the pattern which is directly involved in recognition by, and binding to, the receptor. However, the fact that the existence of this pattern is dependent on a conformation stabilized by intramolecular interactions, ..., implies that other amino acids or sequences contributing to this conformational stability will be no less 'significant' for the biological activity of the molecule.

(p. 5).

And, in conclusion, Rudinger states:

> The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study. The careful design of synthetic analogues, and their evaluation in biological systems which permit separate analysis of the various phases of hormone action, is the best way to obtaining such information.

(p. 6).

Bowie, et al. (1990) Science, 247 : 1306-10 provides similar insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discuses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). In general, Bowie continues to reflect the observations of Rudinger: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only

painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10).

Hence, the nature of the invention is not reasonably predictable for any of the particular proteins and genes claimed, due to the unpredictability of structure-function relationships.

Moreover, if the gene is not within a vector, it will not be delivered and expressed, as it will be destroyed by macrophages and other cells, hence, the Artisan could not predict that simple delivery of the gene would be efficacious.

Further, the gene must be operably linked to a promoter and other transcription/translation signals required for expression and other effects, such as secretion, to allow for the action of the protein. It is clear that a protein that is not secreted will not reach the cells to which immunosupression is desired. Moreover, given that the relative levels of these cytokines, etc., are important only within the context of amounts of other genes (see below), such promoter must have the activity level desired, otherwise the Artisan would not be able to reasonably predict that the protein would have the opposite effect of that desired.

The State of the Prior Art

The prior art, drawn to treating kidney disease, was similarly non-enabling of new inventions.

Tomasoni, et al. (2004) Current Gene Therapy, 4: 115-22, provides a recent overview of such therapy. First, Tomasoni recognizes the barriers which a vector must traverse to target the specific tissues, which must be assessed in order to use them experimentally (p. 115, col. 1, paragraph), thereby recognizing the various aspects of gene therapy in the nature of the invention. Moreover, toxicity, immunogenicity, and efficiency are other aspects which may

preclude any particular vector use (Id., paragraph 2). Further each vector type discussed contains various problems and advantages, and therefore, any particular vector is not reasonably predicted to produce enough of an effect for a long enough time. For example, some retroviral vectors will not transducer non-dividing cells (e.g., p. p. 117, paragraph 3) and special preparation protocols are required for others to transducer particular types of cells of the kidney (Id., col. 2, paragraph 3). Moreover, particular genes claimed are noted to exacerbate particular kidney conditions which suffer from inflammation (e.g., p. 118, paragraph bridging columns). Hence, any particular gene in Applicant's genera would not be predicted to treat any particular condition. Moreover, problems exist with the transient nature of gene expression (p. 119, last paragraph), hence, any prevention method suffers from problems with identification of individuals before they have the disorder. Lastly, Tomasoni concludes with a clear indication that the gene therapy for renal disease is a long way from being reasonably predictable. To wit, gene delivery is the major hurdle, and while looking feasible, studies are needed to establish if the present studies, carried out in rodents will extrapolate to larger animals (p. 120, col. 2, paragraph 2). Moreover, the identification of the causes of the various disorders are still required to identify the defective genes and be able to target them (Id.). Concluding, Tomasoni states "Much basic research is needed before genes transfer can be added to the therapeutic armamentarium for human kidney diseases." (Id.)

Hence, from Tomasoni, it is clear that the present state of the art is not reasonably predictive of the vast majority of animals, that much more research needs to be done before any such therapy is enabled.

Moreover, the various cytokines have unpredictable actions, depending on their ratios with other cytokines, and other unknown factors. Each specific cytokine has individual and synergistic and antagonistic effects with other cytokines. Such complicated interactions, without further guidance, would cause the Artisan to not reasonably predict that in any particular therapy of the kidney, that any particular transgene should be used. (Applicant's specification admits this aspect, p. 6, paragraph 0027.)

Further, much of the problem in Applicant's invention appears to be directed at inflammation. Given the number of cell types, and lack of limitation to autologous, such *ex vivo* therapy would not be predicted to anything but exacerbate the problems, due to immunological responses.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose enough to reasonably predict the various aspects reviewed above, the Artisan could not predict, in the absence of proof to the contrary, that such applications would efficacious in any therapeutic treatment.

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention

by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Applicant's Guidance and Direction

Applicant's specification broadly describes nephritis, glomerulosclerosis, IL-10, and induction of animal models of such diseases (pp. 1-3), a broad summary of the invention (pp. 3-4), definitions (pp. 5-8), discussion of glomerulosclerosis (pp. 8-9), broad discussion of gene therapy, including vectors, administration routes, and genes (pp. 9-15), a discussion of dosages (p. 15), delivery systems (pp. 15-16), effects of cytokine expression on glomerulosclerosis (pp. 16-17), and a restatement of administration and vectors (p. 18).

However, such does not allow the Artisan to reasonably predict whether, in any particular kidney disorder, that any particular vector will transform enough cells, or enough of any particular cell will reach the target site, when administered by any particular route, and express enough protein for a long enough period of time, to have an effect, or whether any particular protein derived of any of the immunosupressants or anti-inflammatories, will have enough activity and do so for a long enough period of time to have an effect. Such is further exacerbated when immune responses are exacerbated by use of inflammatory vectors, and further, given any particular anti-inflammatory or immunosuppressant, the specific disorder may be exacerbated, or the amounts of the other cytokines, etc., may be such that the overall effect exacerbates any effect. Lastly, in prevention, such does not allow the artisan to identify those who will get it, and due to attenuation of gene expression, if they are preventatively treated, the gene expression may be attenuated before the onset of the disorder, and hence, they would not be so preventatively treated.

Further Applicant's non-patent literature demonstrates that the results are not reasonably predictive of treatment of other animals, particular humans. To wit, Choi, et al. (2003) Gene Therapy, 10: 559-68 basically discloses all that is in the present application. In concluding, Choi recognizes that while IL-10 treatment would be a logical approach for the prevention of disease progression, it is still not reasonably predicted, and it would be useful to determine if exogenous expression of IL-10 could have similar effects in other animal models of glomerular disease, including humans (p. 565, paragraph bridging columns). Hence, even after the date of invention, Applicant does not reasonably predict the core disclosed invention to be efficacious for treatment in humans, but only in prevention in a particular animal model.

The Examples

Example 1 discloses AdV vectors and mice used in the model of nephritis, which develop nephritis after about 6 weeks of age. Examples 2-3 demonstrate the creation of AdV5 vectors with Il-10 transgene driven by CMV promoter. Example 4 teaches the administration of vector (direct admin to exposed kidney) to mice. Example 5 demonstrates PCR detection of Il-10 transcript. Example 6 demonstrates Evaluation of gene expression. Example 7 demonstrates IL-10 protein assays. Example 8 demonstrates proteinuria assys. Example 9 demonstrates histological analysis. Example 10 demonstrates quantitative PCR. Example 11 demonstrates immunostaining for TGF-beta, Example 12 demonstrates statistical analysis. Example 13 demonstrates efficient transduction of renal tissue with the vectors. Example 14 demonstrates similar transduction in vivo. Example 15 demonstrates inhibition of FSGS by transduction. Example 16 demonstrates reduction of proteinuria. Example 17 demonstrates reduction in TGF-beta1 expression.

These examples demonstrate the delay of onset of the disorder in mice, but such does not reasonably predict treatment, nor does it predict prevention in other animals. In the instant case, the mice were known to develop nephritis, and in real life, for other animals, e.g., humans, such development is not known for when it will develop, and people predisposed are not known. Without further guidance and/or examples, treatment or prevention in humans would not be predicted.

Undue Experimentation

Because the Artisan would have to perform undue experimentation to determine if any particular transgene, in any particular vector, and using any particular promoter and other expression elements, would, via any particular administration route, transform enough cells, produce enough stable and functional mRNA and protein therefrom, and that protein would reach its site of action in large enough amounts for a long enough period of time, to have a therapeutic effect, the Artisan would not find Applicant's claims enabled, absent undue experimentation.

Conclusion

Due to the undue experimentation, Applicant's claims are not enabled.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633
2C55 Remsen Building
(571) 272-0729